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REPLY BRIEF UNDER 37 C.F.R. §41.41 Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket Confirmation No.	IRVN-263CIP 4882
	First Named Inventor	J.S. Reid
	Application Number	09/739,933
	Filing Date	December 18, 2000
	Group Art Unit	1649
	Examiner Name	S.L. Turner
	Title	*Compositions and Methods for Manipulating Glial Progenitor Cells and Treating Neurological Deficits*

Sir:

This Reply Brief is responsive to the Examiner's Answer mailed July 12, 2005. The Examiner's Answer required a response within two months from the mailing date, or on or before September 12, 2005. Accordingly, this Reply Brief is timely filed.

A Request for Oral Hearing is filed as a separate paper accompanying this Reply Brief, as required by 37 C.F.R.§41.47.

The Commissioner is hereby authorized to charge deposit account number 50-0815 in the amount of $ 500.00 to cover the fee required under 37 C.F.R. §41.20(b)(3) for filing Appellants' Request for Oral Hearing, which submitted with this filing in a separate paper. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§1.17, 41.41, and 41.47 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number IRVN-263 CIP.

In view of the remarks set forth below, reconsideration and allowance are respectfully requested.

I. REMARKS

A. INTRODUCTORY COMMENTS

The claims on appeal have been rejected as being anticipated under 35 U.S.C. §102(e) and as being obvious under 35 U.S.C. §103(a) over U.S. Patent. No. 5,980,885 to Weiss et al. (hereinafter "Weiss" or "the Weiss patent"). Appellants respectfully submit that these rejections are unsupported by either the law, or an objective reading of the Weiss patent.

The Examiner's reasoning in support of these rejections is not sound. The grounds for these rejections require:

1) determining that disclosure of a genus anticipate a species under 35 U.S.C. §102(e), contrary to the law;
2) ignoring the direct teaching in Weiss that, where growth factor polypeptides are to be administered, they are administered to the ventricles (the opposite of what is claimed), and support the citation of Weiss in the rejections under §§102(e) and 103(a);
3) equating use of cells with the use of growth factor polypeptides, contrary to the teaching in Weiss, to support the reading of Weiss required to sustain the rejections under §§102(e) and 103(a);
4) "picking and choosing" bits of disclosure from various parts of Weiss, and combine these bits in a manner both contrary to the law and the teachings of Weiss itself, to find support for the grounds of the rejection under both §§102(e) and 103(a);
5) finding motivation to modify Weiss' instructions relating to administration of polypeptides by substituting Weiss' instructions relating to administration of cells, in order to support the rejection under §103(a);
6) finding that Weiss provides a reasonable expectation of success in practicing the claimed invention, where Weiss shows only administration of growth factors *other than TGF-α* *and* *administers these growth factors to the ventricles*, in order to support the rejection under §103(a).

The Examiner's Answer also contains other errors in interpretation of claim terms, which are not supported by sound reasoning, which are addressed in detail below.

If one attempts to read Weiss in the context of the claimed invention, Weiss at best, discloses, teaches, and enables nothing except a manner of transplanting cells into a damaged brain, and administration, in a manner not specified, of an unspecified combination of growth factors, into the ventricles of a damaged brain. Thus, Weiss has no bearing upon the instant Application, which specifies the administration of Transforming Growth Factor-α into locations other than the ventricles of a damaged brain. A careful reading of the Weiss patent without the use of hindsight reconstruction of the claimed invention, reveals that Weiss does not disclose or suggest the claimed invention directed to administration of TGF-α or functional fragments thereof *parenterally and outside the ventricles. **Weiss teaches that where a growth factor polypeptide is to be administered, it must be administered*** **inside the ventricles; the only teaching to parenterally administer any substance outside the ventricles is the administration of *cells.* *Weiss does not place the claimed invention into the hands of the public.***

Appellants have not reiterated all prior arguments and comments of the Appeal Brief. This is neither necessary nor desirable as it is not the purpose of a Reply Brief.[1] Instead, Appellants' Reply Brief provides:

1) a subsection entitled the THE ISSUES ON APPEAL, which provides additional basis in the law supporting Appellants' positions that the claimed invention is neither
   (a) anticipated by Weiss et al. (U.S. Patent No. 5,908,885; "Weiss") under 35 U.S.C. §102(e); nor
   (b) rendered obvious by Weiss under 35 U.S.C. §103(a);

and

2) a subsection entitled THE EXAMINER'S ANSWER, which addresses particular comments in the Examiner's Answer which are erroneous.

[1] Appellants note that all prior positions and arguments as set out throughout the prosecution history of the present case, including as set out in the Appeal Brief, are maintained. Failure to reiterate all arguments, for the sake of brevity, in the present Brief is not meant to imply concession on any prior position or argument.

B. THE ISSUES ON APPEAL

Two issues remain on appeal:

1. **WHETHER THE CLAIMED INVENTION IS ANTICIPATED UNDER 35 U.S.C.§102(E) BY WEISS ET AL. (U.S. PATENT NO. 5,980,885; "WEISS");**

and

2. **WHETHER THE CLAIMED INVENTION IS OBVIOUS UNDER 35 U.S.C. §103(A) IN VIEW OF WEISS**

All pending claims stand rejected under each of these issues. Appellants note with gratitude the withdrawal of the rejection of claims 2, 3, 5 and 20 under 35 U.S.C. §112, ¶2.

1. WEISS DOES NOT ANTICIPATE THE CLAIMED INVENTION UNDER 35 U.S.C. §102(E)

Claims 1-3, 5-8, 33, 63, and 64 were rejected under 35 U.S.C.§102(e) as allegedly anticipated by Weiss et al. (U.S. Patent No. 5,980,885; "Weiss").

a. Weiss At Best Discloses A Genus Of Growth Factors For Administration To A Genus Of Sites

Appellants' invention is focused. It requires

1) administering a specific growth factor: TGF-α polypeptide– or a functional fragment of TGF-α.;
2) delivery of the TGF-α to a specific location – outside the ventricles and accessible in the area of neuronal damage (i.e. the injury signal and TGF-α must overlap in the brain tissue outside the ventricles).
3) the TGF-α must be delivered to the correct site of administration in amounts needed to obtain a desired result.

Even an extremely generous and broad reading of Weiss shows that Weiss:

1) refers to "growth factors" in general, and even goes so far as to "teach" use of "any growth factor known in the art"[2]; and

2) refers to delivery of unspecified growth factors to various places within the ventricles;

The "disclosure" of Weiss, if it discloses anything, is a disclosure of a genus of growth factors and a genus of administration sites. It is well-settled that "earlier disclosure of a genus does not necessarily prevent patenting a species member of the genus."[3] There is simply no disclosure of the specific species of the claims, i.e., parenterally administering *TGF-α polypeptide* or a functional fragment thereof *to a site outside the ventricles*.

If Weiss is read as the Examiner advocates, with all administration sites used for cells useful for growth factor polypeptides (a reading which is unsupported by the law, as discussed below), then Weiss is, at best, a very broad generic disclosure, which no disclosure of the species that is subject matter of the appealed claims.[4] Appellants have claimed a specific species. The genera disclosed in Weiss do not anticipate this species. On this basis alone the rejection of the claims under 35 USC § 102(e) should be reversed.[5]

b. Weiss Discloses Administration of Growth Factor Polypeptides Into the Ventricles, *NOT* Parenterally, Outside The Ventricles As Required By The Appealed Claims

The Examiner's position that Weiss provides each and every limitation of the claimed invention, and thus anticipates the appealed claims, is not based upon a reading of Weiss as a whole and is, to state

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[2] Weiss, col. 25, lines 27-29. Appellants note that growth factors are not interchangeable, but rather attach to different receptors with different effects. Weiss' "teaching" of "growth factors" is thus incredibly overly broad, and fails to point the reader to use of any one growth factor, including the use of TGF-α as per the claimed invention.

[3] See, e.g., *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1380, (Fed. Cir. 2001); *Lilly v. Board of Regents*, 67 USPQ 2nd 1161 at 1165 (Fed. Cir. 2003); and *Metabolite Laboratories Inc. v. Laboratory Corp. of America Holdings*, 71 USPQ2d 1081 (CA FC 2004).

[4] Moreover, if the Weiss patent is read as advocated by the Examiner, Weiss as a reference would effectively squelch any and all future claims that would result from any future research using any growth factor to repair damage in a mammalian brain. Given the vagueness of Weiss and the generic nature of its disclosure, this simply cannot be the case.

[5] See, e.g., *Eli Lilly Co. v. Board of Regents*, 67 USPQ 2d 1161 (Fed. Cir. 2003).

it plainly, simply incorrect. Weiss does not disclose or suggest administration of TGF-α (or any other growth factor polypeptide), to a site *outside the ventricles* as required by the appealed claims.

Instead, Weiss repeatedly emphasizes that their invention is advantageous *because Weiss' invention provides for modification of cells* ***surrounding the ventricles:*** (col. 25, line 16 - col. 26, line 16):

> The fact that neural stem cells are located in the tissues lining ventricles of mature brains offers several advantages for the modification and manipulation of these cells in vivo and the ultimate treatment of various neurological diseases, disorders, and injury that affect different regions of the CNS. Therapy for these can be tailored accordingly so that stem cells surrounding ventricles near the affected region would be manipulated or modified in vivo using the methods described herein. The ventricular system is found in nearly all brain regions and thus allows easier access to the affected areas. If one wants to modify the stem cells in vivo by exposing them to a composition comprising a growth factor or a viral vector, it is relatively easy to implant a device that administers the composition to the ventricle and thus, to the neural stem cells. For example, a cannula attached to an osmotic pump may be used to deliver the composition. Alternatively, the composition may be injected directly into the ventricles. The neural stem cell progeny can migrate into regions that have been damaged as a result of injury or disease. Furthermore, the close proximity of the ventricles to many brain regions would allow for the diffusion of a secreted neurological agent by the stem cells or their progeny.

(emphasis added)

Weiss also addresses treatment of specific conditions: (col. 26, lines 17-22):

> For treatment of Huntington's Disease, Alzheimer's Disease, Parkinson's Disease, and other neurological disorders affecting primarily the forebrain, growth factors or other neurological agents would be delivered to the ventricles of the forebrain to affect in vivo modification or manipulation of the stem cells.

(emphasis added)

Finally, *Weiss distinguishes their invention from the prior art* by emphasizing that *Weiss' invention can be accomplished by administration of "growth factors"* **to the ventricles**:[6]

> Prior art methods for treating Parkinson's disease usually involves the use of the drug L-Dopa, to raise dopamine levels in the striatum. However, there are disadvantages with this treatment including drug tolerance and side effects. Also, embryonic tissues that produce dopamine have been transplanted into the striatum of human Parkinsonian patients with reasonable success. However, the use of large quantities of fetal human tissue required for this procedure raises serious ethical concerns and practical issues.
>
> The methods and compositions of the present invention provide an alternative to the use of drugs and the controversial use of large quantities of embryonic tissue for treatment of Parkinson's disease. Dopamine cells can be generated in the striatum by the administration of a composition comprising growth factors to the lateral ventricle. A particularly preferred composition comprises a combination of EGF, FGF-2, and heparan sulphate. The composition preferably also comprises serum..

(emphasis added)

Weiss thus emphasizes that administration of "growth factors" ***to the lateral ventricle*** provides an ***alternative*** to prior art methods which involve administration embryonic tissues ***to the striatum***. Weiss similarly describes treatment of specific conditions as involving delivery of "growth factors" within the ventricular space:[7]

> For the treatment of MS and other demyelinating or hypomyelinating disorders, and for the treatment of Amyotrophic Lateral Sclerosis or other motor neuron diseases, growth factors or other neurological agents would be delivered to the central canal.
>
> In addition to treating CNS tissue immediately surrounding a ventricle, a viral vector, DNA, growth factor, or other neurological agent can be easily administered to the lumbar cistern for circulation throughout the CNS.

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[6] Weiss, col. 26, lines 30-46.

[7] Weiss, Col. 26, lines 57-65.

Appellants note that Weiss defines "ventricle" as "any cavity or passageway within the CNS through which cerebral spinal fluid flows", and encompasses "the lateral, third and fourth ventricles, and the central canal, cerebral aqueduct, and other CNS cavities."[8] Thus, once again, **Weiss fails to direct parenteral administration of growth factor polypeptides** to a site **outside the ventricles**, as required by the appealed claims.

Reading Weiss as providing instruction to administer growth factor polypeptides into the ventricles is consistent with the working examples of Weiss. This *includes* Examples 27-30, the very Examples upon which the Examiner relies for support of the rejections. In Example 27, EGF is administered to the lateral ventricles (col. 47, lines 12-17). In Example 28, EGF and FGF are administered into ventricle III of the diencephalons, ventricle IV of the brain stem and central canal of the spinal cord. (co. 37, lines 56-63). In Example 29, EGF and FGF are administered into the fourth ventricle. (col. 48, lines 27-33).

None of Examples 27-30 support the proposition for which they are asserted: none of these examples teach administration of a growth factor *anywhere* except *to the ventricles.* Appellants find no direction in any of these Examples to administer ***TGF-α*** or a fragment thereof ***outside the ventricles***, as required by the appealed claims.

In further attempts to support the rejections of the claims, the Examiner's Answer states:[9]

> Weiss is not limited to ventricular administration of growth factor. For example, Weiss teaches administration other than in the ventricle, see in particular oral administration, injection, injection cannula, timed release apparati at the desired site, see in particular column 25, line 20-column 26, line 15. New claim 1 as amended recites parenteral administration. Parenteral administration refers to administration

As discussed in more detail below, Weiss' fleeting disclosure of oral administration is irrelevant, since the appealed claims require "parenterally" administering.[10] Appellants submit that Weiss states

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[8] Weiss, col. 13, lines 4-11.

[9] Examiner's Answer, page 7.

[10] This point is discussed in more detail below in response to the Examiner's interpretation of the term "parenteral".

"injection, injection cannulae, and timed release apparati" for administration of "growth factors", but Weiss is not specific about what growth factor(s) to use. Weiss treats all growth factors as fungible.[11] But this disclosure is not sufficient to provide the claimed invention: *Where in the subject should the injection cannula be positioned? Into what site should the injection be administered? What site is desired for placement of the "timed release apparati"?*

According to the Examiner's overly generous (and, in Appellants' view, erroneous) reading of Weiss, Weiss teaches administration of any and all growth factors by any and all routes, by any and all methods. Appellants' respectfully submit that the Examiner's reliance on the "disclosure" of oral administration above exemplifies the kind of flawed logic upon which the rejections are based. Under such reasoning, a reference which provided a laundry list of "growth factors" and a laundry list of "administration sites" would be sufficient to provide an anticipatory disclosure of any and all combinations of any and all growth factors administered to any and all sites in a subject. It is well-settled that in order to anticipate, "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim."[12]

Again Weiss, at best, discloses only a *genus* of **possible** administration sites in this context. The appealed claims are directed to a species of this genus. As discussed at length above, a "genus" cannot anticipate a species. Furthermore, if the ordinarily skilled artisan considered this selected passage in Weiss ***in the context of all other guidance in Weiss relating to administration of growth factor polypeptides, the skilled artisan would administer those polypeptide into the ventricles, NOT outside the ventricles*** as does the claimed invention.

c. Guidance in Weiss Relating to Administration of Cells Cannot Be Applied to Administration of Growth Factor Polypeptides

In support of the rejection of the claims, the Examiner's Answer points to disclosure in Weiss that relates to administration of ***cells. The Examiner then equates administration of cells with administration of growth factors.*** The Examiner goes on to conclude that administration sites and routes disclosed in Weiss for administration of cells can thus be applied to administration of growth factor polypeptides.

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[11] See Weiss, col. 25, line 20 to col. 26, line 15.

[12] Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The Examiner's reading of Weiss is not only unsupported by the law,[13] but is also inconsistent with statements in the Weiss reference itself. Appellants again point out that Weiss distinguishes the prior art from their invention by emphasizing that Weiss' invention can be accomplished by administration of "**growth factors**" **to the ventricles**:[14]

> Prior art methods for treating Parkinson's disease usually involves the use of the drug L-Dopa, to raise dopamine levels in the striatum. However, there are disadvantages with this treatment including drug tolerance and side effects. Also, embryonic tissues that produce dopamine have been transplanted into the striatum of human Parkinsonian patients with reasonable success. However, the use of large quantities of fetal human tissue required for this procedure raises serious ethical concerns and practical issues.
>
> The methods and compositions of the present invention provide an alternative to the use of drugs and the controversial use of large quantities of embryonic tissue for treatment of Parkinson's disease. Dopamine cells can be generated in the striatum by the administration of a composition comprising growth factors to the lateral ventricle. A particularly preferred composition comprises a combination of EGF, FGF-2, and heparan sulphate. The composition preferably also comprises serum..

Thus, in distinguishing their invention from the prior art, the Weiss reference itself points out the ***difference in routes of administration for growth factor polypeptides and cells. Indeed, Weiss describes administration of growth factor polypeptides into the ventricles as an alternative to administration of cells outside the ventricles.***

Finally, the Examiner also points to Appellants' specification in support of its position that administration of growth factor polypeptides and administration of cells can be treated as equivalent. Specifically, at page 9 of the Examiner's Answer, and after an extensive discussion of Weiss' disclosure relating to administration of *cells*, the Examiner points to Appellants' disclosure of gene therapy vector administration.

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[13] See discussion below about the prohibition against "picking and choosing" elements in the prior art.

[14] Weiss, col. 26, lines 30-46.

How this portion of Appellants' specification supports the Examiner's argument is, not clear. The Examiner seems to suggest that equating the disclosure by Weiss of administration of cells to deliver a growth factor with administration of growth factor polypeptide *per se* is supported by Appellants' disclosure relating to administration of gene therapy vectors in lieu of administration of growth factor polypeptide.

This reasoning suffers from more than one failure of logic. First, it would require conflating the Weiss disclosure and Appellants' specification, and then construing Appellants' claims in light of this improperly combined disclosure. This is an approach to claim construction for which Appellants can find no basis in the law. Second, Appellants' own specification's teaching of parenteral administration of gene therapy vectors is consistent with administration of TGF-α polypeptides to parenteral sites. This disclosure in no way undermines Appellants' position that **in the *Weiss* reference, where it refers to growth factors at all, it specifically requires administration of growth factor polypeptides *to the ventricles*.**

d. The Rejections of the Claims Rely Upon "Picking and Choosing" from the Disclosure of Weiss, In Direct Contradiction to the Law and The Disclosure of Weiss Itself

The Examiner's reasoning in support of rejections of the appealed claims requires cutting various disclosures from the fabric of Weiss, and re-stitching them together to provide the patchwork quilt that constitutes the Examiner's rejections. For example, as discussed above, the Examiner's Answer points to disclosure in Weiss that relates to administration of ***cells***, and then equates administration of cells with administration of growth factors. Based on this "cells-equal-growth-factors and all growth factors are the same" assumption, the Examiner goes on to conclude that routes disclosed in Weiss for administration of cells can be applied to administration of growth factor polypeptides.[15]

[15] Appellant notes that this is in direct contradiction to the teaching in Weiss, as discussed above. Weiss distinguishes their invention from the prior art by stating that administration of growth factor to the ventricle provides an alternative to the prior art administration of cells.

The Examiner points to portions of Weiss that discuss administering cells into a site of CNS damage, and combines such disclosures with discussion of administering growth factors into the ventricles. For example, the Examiner states:

> "In particular Weiss teaches injection of growth factors to animals having CNS damages or lesion, see in particular column 22, lines 10-17." (Examiner's Answer, page 6)
>
> and
>
> "Weiss teaches multiple methods of growth factor administration including via mechanisms in addition to direct in vivo administration. For example column 10, lines 23-column 11, line 4, teach that the administration may be via culture of cells with TGF-alpha, via transplantation of cells maintained or produced under such culture conditions, or via genetic manipulation of cells to provide the growth factor to the host either in vitro or in vivo. The claims further specify that preferred areas suitable for transplantation of such cells either supported by TGF-alpha or which produce TGF-alpha are to areas of CNS brain tissue including the striatum, adjacent to the ventricle (the subependymal zone), and to the spinal tissue, see in particular column 12, line 53-column 13, line 41. (Examiner's Answer, bridging paragraph, pages 7-8)

At each citation to Weiss cited in support of the Examiner's position, Weiss discusses administration of cells, *not* a TGF-α polypeptide. Indeed, the section at column 22, lines 10-17 is under the heading "Transplantation of *Neural Stem Cell Progeny* Alleviate Disorders of the CNS in Animal Models Caused by Disease or Injury."[16] At column 10, line 23 to column 11, line 4, Weiss primarily discusses administering cells. At column 12, line 53 to column 13, line 41, Weiss discusses obtaining cells from a donor.

The Examiner then points to Weiss at "column 25, line 20-column 26, line 15."[17] In this section, which is under the heading "In Vivo Proliferation, Differentiation, and Genetic Modification of *Neural*

[16] Weiss, column 21, lines 48-51.

[17] Examiner's Answer, page 7.

Stem Cell Progeny," Weiss discusses administration of growth factors *into the ventricles*.[18] For example, Weiss states:

1) "The ventricular system is found in nearly all brain regions and thus allows easier access to the affected areas. If one wants to modify the stem cells in vivo by exposing them to a composition comprising a **growth factor** or a viral vector, it is relatively easy to implant a device that administers the composition **to the ventricle** and thus, to the neural stem cells. For example, a cannula attached to an osmotic pump may be used to deliver the composition. Alternatively, composition may be injected directly **into the ventricles.**" (Weiss, column 26, lines 2-10; emphasis added);

2) "For treatment of Huntington's Disease, Alzheimer's Disease, Parkinson's Disease, and other neurological disorders affecting primarily the forebrain, **growth factors** or other neurological agents would be delivered **to the ventricles** of the forebrain to affect in vivo modification or manipulation of stem cells" (Weiss, column 26, lines 15-21; emphasis added);

3) "Dopamine cells can be generated in the striatum by the administration of a composition comprising **growth factors to the lateral ventricle**. (Weiss, column 26, lines 41-43; emphasis added);

4) "For the treatment of MS and other demyelinating or hypomyelinating disorders, and for the treatment of Amyotrophic Lateral Sclerosis or other motor neuron diseases, **growth factors** or other neurological agents would be delivered **to the central canal**" (Weiss, column 26, lines 57-50; emphasis added); and

5) "In addition to treating CNS tissue immediately surrounding a ventricle, a viral vector, DNA, **growth factor**, or other neurological agent can be easily administered **to the lumbar cistern** for circulation throughout the CNS" (Weiss, column 26, lines 61-64; emphasis added).

Appellants submit that this reading is not supported by the law.[19] The Examiner's rejections require that Weiss' disclosure of routes of administration of *cells* be substituted for Weiss' disclosure of routes of administration of *growth factor polypeptides*. However, such mixing and matching of

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[18] Weiss further emphasizes the importance of ventricles as a site of administration in providing a definition for "ventricle." Weiss defines "ventricle" as "any cavity or passageway within the CNS through which cerebral spinal fluid flows" (which would include the lumbar cistern); furthermore, Weiss states that the term "ventricle" encompasses the lateral, third, and fourth ventricles, and the central canal, cerebral aqueduct, and other CNS cavities. Weiss, column 13, lines 4-11.

[19] See discussion below about the prohibition against "picking and choosing" elements in the prior art.

disclosure is not permissible. In order for a rejection under 35 U.S.C.§102(e) to be proper, the cited reference must clearly and unequivocally disclose the claimed invention "without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."[20]

Not only is the Examiner's reading of Weiss improper under the law as set out above, but it is also inconsistent with statements in the Weiss reference itself. Again we note that Weiss distinguishes their invention from the prior art by emphasizing that Weiss' invention involves administration of "growth factors" **to the ventricles**.[21] Thus the Weiss patent itself acknowledges that, in the context of their disclosed invention, ***there is a difference in sites of administration for growth factor polypeptides and for cells. Weiss regards administration of growth factor polypeptides into the ventricles as an alternative to administration of materials (e.g., cells) outside the ventricles.***

e. Conclusion

The rejection of claims 1-3, 5-8, 33, 63, and 64 under 35 U.S.C. §102(e) is in error. Weiss does not disclose a method as claimed, comprising administering a TGF-α polypeptide or a functional fragment thereof to an individual having a central nervous system (CNS) damage or lesion, where the TGF-α polypeptide or functional fragment thereof is administered to a site **outside the ventricles**. Weiss does not teach each and every claim element. Accordingly, Weiss cannot anticipate the appealed claims.

2. WEISS DOES NOT RENDER THE CLAIMED INVENTION OBVIOUS UNDER 35 U.S.C. §103(A)

The rejection of claims 1-3, 5-8, 33, 63, and 64 under 35 U.S.C.§103(a) is in error for several reasons. Many of these reasons are discussed above in the context of the rejection under 35 U.S.C. §102(e), and apply with equal force here. For example, "picking and choosing" from the disclosure of Weiss in order to substitute sites for administration of cells for the sites for administration of growth factor polypeptides and arrive at all elements of the claimed invention is not within the proper application of the relevant law, and further not supported by the Weiss reference itself.

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[20] *In re Arkley* 172 USPQ 524 (CCPA, 1972).

[21] Weiss, col. 26, lines 30-46.

The Examiner has failed to set out a *prima facie* case of obviousness for at least the following reasons:

- Weiss provides no motivation to modify its teachings relating to growth factor polypeptides with the teaching relating to administration of cells.
- Weiss does not provide a reasonable expectation of success that administration of a TGF-α polypeptide or functional fragment thereof to a site outside the ventricles in an individual having a CNS damage or lesion will have the effect recited in Appellants' claims (i.e., to affect migration of a neural progenitor cell or progeny thereof away from the ventricles and toward the site of CNS damage or lesion). All examples of Weiss relating to growth factor polypeptide administration involve administration to the ventricles -- and do not even involve use of TGF-α or a functional fragment thereof.

As discussed above, Weiss states that the Weiss invention is advantageous *because Weiss' invention provides for modification of cells* ***surrounding the ventricles.***[22] Weiss distinguishes the prior art from their invention by pointing out that Weiss' invention involves administration of "growth factors" **to the ventricles.** We again provide this disclosure for convenience:[23]

> Prior art methods for treating Parkinson's disease usually involves the use of the drug L-Dopa, to raise dopamine levels in the striatum. However, there are disadvantages with this treatment including drug tolerance and side effects. Also, embryonic tissues that produce dopamine have been transplanted into the striatum of human Parkinsonian patients with reasonable success. However, the use of large quantities of fetal human tissue required for this procedure raises serious ethical concerns and practical issues.
>
> The methods and compositions of the present invention provide an alternative to the use of drugs and the controversial use of large quantities of embryonic tissue for treatment of Parkinson's disease. Dopamine cells can be generated in the striatum by the administration of a composition comprising growth factors to the lateral ventricle. A particularly preferred composition comprises a combination of EGF, FGF-2, and heparan sulphate. The composition preferably also comprises serum.

[22] Weiss, col. 25, line 16 - col. 26, line 16.

[23] Weiss, col. 26, lines 30-46.

Weiss thus emphasizes that administration of "growth factors" ***to the lateral ventricle*** provides an ***alternative*** to prior art methods which involve administration of embryonic tissues ***to the striatum***. Weiss not only does not disclose the claimed invention, it actually points the skilled artisan in a direction ***away*** *from the claimed invention.*

Weiss' instruction to deliver a "growth factor" to the ventricles is carried out in each of the Examples 27-30. In Example 27, EGF is administered to the lateral ventricles.[24] In Example 28, EGF and FGF are administered into III ventricle of the diencephalons, IV ventricle of the brain stem and central canal of the spinal cord.[25] In Example 29, EGF and FGF are administered into the fourth ventricle.[26] **None of Examples 27-30 support the proposition for which they are asserted by the Examiner – none of these examples teach administration of a growth factor *anywhere* except *to the ventricles.*** Appellants find no direction in any of these Examples to administer ***TGF-α*** or a fragment thereof ***outside the ventricles***, as required by the appealed claims.

Accordingly, the Examiner has not established a prima facie case of obviousness, and therefore the claims are not rendered obvious by Weiss.

C. THE EXAMINER'S ANSWER

Appellants now turn to specific elements of the Examiner's Answer which they believe merit a specific response. These includes 1) the assertion that the Summary of Invention in Appellants' Appeal Brief is deficient; and 2) the interpretation of "parenteral" to include "oral" based on the Examiner's reading of Appellant's specification.

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[24] Weiss, col. 47, lines 12-17.

[25] Weiss, col. 37, lines 56-63.

[26] Weiss, col. 48, lines 27-33.

1. SUMMARY OF INVENTION

The Examiner's Answer stated that the Summary of Invention contained in Appellants' Brief is deficient because "it does not refer to the other modes or routes of administration intended to be encompassed, in particular with respect to 'parenteral administration' as claimed."[27]

As set forth in 37 C.F.R.§41.37, an Appeal Brief must contain a summary of the **claimed** subject matter on appeal.[28]

The Examiner's Answer characterized pages 33-37 of Appellants' specification as referring to alternative routes of administration "inclusive of in vitro, in vivo and via genetic manipulation." However, the **claimed** subject matter relates to administering a **TGF-α polypeptide** or a functional fragment thereof, wherein the administration is **outside the ventricles** (e.g., parenteral or, more specifically, intrastriatal). Although Appellants' specification may disclose administering a substance other than a TGF-α **polypeptide** or functional fragment thereof, and may disclose other routes of administration such as oral, **these limitations are not present in the claims.** The **claimed** subject matter relates to administering a TGF-α polypeptide or functional fragment thereof, as recited, where the administration is outside the ventricles. An interpretation of the claimed subject matter that requires ignoring limitations of the claims is improper.

2. PARENTERAL ADMINISTRATION

The Examiner's Answer states that "Appellant's specification places oral administration, as in Weiss, within the 'parenteral' route and thus Weiss anticipates."[29] Apparently, the Examiner's position is that if Appellants' specification can be construed such that parenteral administration encompasses oral administration, then Weiss anticipates the appealed claims.

Not only is the Examiner's reading of Appellants' specification improper under the law, but it is also an incorrect reading of Appellants' specification and of the Weiss patent.

Words in patent claims are to be given their ordinary meaning according to their use in the field of the invention, *unless* the text of the patent makes clear that a word has a different special meaning.

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[27] Examiner's Answer, page 3.

[28] 37 C.F.R.§41.37(a)(2)(c)(v) (stating "A concise explanation of the subject matter defined in each of the independent claims involved in the appeal...")

[29] Examiner's Answer, page 7.

Toro Co. v. White Consol. Indus., Inc., 199 F.3d 1295, 1299 53 USPQ2d 1065, 1067 (Fed. Cir. 1999). As stated in MPEP §2111.01 (III):

> and drawings"). Any< special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). See also *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) and MPEP § 2173.05(a).

(emphasis added)

Appellants' specification does not assign any special meaning to "parenteral" that is different from its ordinary and customary meaning. Appellants' specification states:

> Those of ordinary skill in the art appreciate the need to formulate pharmaceutical compositions for their intended route of administration (which may include **parenteral, *e.g.*,** intravenous, intradermal, or intramuscular injection; oral administration; or direct application to the affected area). It is contemplated that the present methods will be carried out by applying polypeptides to neural precursors harvested from the brain and placed in culture or directly to the precursor cells *in vivo* (by, *e.g.*, infusion through an injection cannula or shunt, or by implantation within a carrier, *e.g.*, a biodegradable capsule) but other routes of administration, particularly parenteral (preferably intravenous) administration, are also within the scope of the invention.[30]

(emphasis added)

The specification points to parenteral administration and provides three examples: intravenous, intradermal or intramuscular injection. A semicolon (;) denotes the end of the list of examples of parenteral administration. According to the rules of English grammar, a semicolon can function to separate units or elements of a series, particularly if one or more units in the series contain commas. Oral

[30] Specification, page 34, lines 9-17.

administration is listed *after* the semicolon. Oral administration is clearly *not* intended as an example of parenteral administration.

Even if there is disagreement about the meaning and use of the semicolon in this passage, it can not reasonably be said that the passage is sufficient clear to support a meaning of parenteral that is a "departure form common usage would be understood by a person of experience in the field of the invention." As discussed in the Appeal Brief, "parenteral" normally means "not enteral", which is the *opposite* of oral. Any attempt to assert that "parenteral" encompass oral administration would be tantamount to ascribing a meaning to "parenteral" that is contrary to the ordinary and customary meaning of "parenteral." Surely more than the relative positioning of punctuation marks in a short passage must be required to ascribe a meaning to "parenteral" administration that is so repugnant to its normal use. Appellants specification, if reasonably read, does not provide any support for reading "parenteral" to encompass "oral" and take on such a bizarre meaning.

3. ADMINISTRATION OF A TGF-A POLYPEPTIDE INTO THE VENTRICLES DOES NOT RESULT IN MIGRATION OF NEURAL STEM CELLS OR PROGENY TO A SITE OF CNS LESION OR DAMAGE.

Administration of TGF-α into the ventricles simply does not induce significant migration of neural progenitor cells or progeny thereof toward a site of CNS injury.[31] There are a number of barriers between the ventricles and the brain tissue outside the ventricles. Neural stem cells resident within the ventricles normally migrate through the ventricles toward the olfactory bulb, and do not typically migrate through these barriers into the brain tissue outside the ventricles.

The Examiner has repeatedly pointed to Example 27 of Weiss in support of its rejections of the claims. Example 27 describes an experiment in which a growth factor, *epidermal growth factor (EGF)*, was administered *into the lateral ventricles* and *in vivo* proliferation of neural stem cells of the lateral ventricle assessed. A recombinant retrovirus containing a β-galactosidase gene ("β-gal retrovirus") was injected into the forebrain lateral ventricles of CD1 adult male mice as a "reporter" of cellular proliferation or migration.[32] Osmotic mini-pumps filled with EGF were surgically implanted *into the*

[31] Specification, page 57, lines 7-11.

[32] Weiss, column 46, line 66 to column 47, line 2.

lateral ventricles on the same day that the β-gal retrovirus was injected.[33] Six days following initiation of EGF infusion, the mice were sacrificed, and the brains were processed for histochemical assays for β-gal activity.[34]

Weiss described the results of this experiment as follows:

1) infusion of *EGF alone* resulted in an expansion of the population of β-gal labeled cells *from 20 cells per brain up to an average of 150 cells per brain*, and migration of these cells away from the ventricles;
2) infusion of FGF-2 resulted in an increase in the number of β-gal labeled cells, but this increase was not accompanied by migration; and
3) *infusion of EGF and FGF together* resulted in an expansion of β-gal labeled cells from *20 cells per brain to an average of 350 cells per brain*.

Weiss does not describe administration of TGF-α or a functional fragment thereof in this example, nor does the animal in this example have any CNS damage or lesion. Further, administration of EGF alone only provided for an increase from 20 cells to 150 cells; administration of *both* EGF and FGF only provided for an increase from 20 cells to 350 cells.

In contrast, Appellants' specification shows that administration of TGF-α into the ventricles did not cause formation of a striatal ridge, which indicates there was no significant migration of neural progenitor cells away from the ventricles.[35] The inventors have also shown in a subsequent publication that administration of *TGF-α outside the ventricles in a brain having a lesion* induces *proliferation and migration of **millions** of cells* to the locus of damage.[36]

Even Weiss notes that, the observed "increase" [e.g., from 20 cells per brain to up to an average of 150 cells per brain, as discussed in Weiss, column 27, lines 3-9] is on the order of "background

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[33] Weiss, column 47, lines 12-16.

[34] Weiss, column 47, lines 24-42.

[35] Specification, page 57, lines 8-11; and page 72, lines 17-19.

[36] See Fallon et al. (2000) *Proc. Natl. Acad. Sci. USA* 97:4686:14691 (copy submitted as Exhibit 2 with Appellants' Appeal Brief, and with response filed July 22, 2003).

noise." Example 27, nor any other Example or disclosure in Weiss teaches or suggests any different therapy or any different result. Weiss simply does not place the claimed invention into the hands of the public, and as such can not render the claimed invention obvious.

4. THE §103(A) REJECTION RELIES ON THE SAME IMPROPER SUBSTITUTION OF SITES OF ADMINISTRATION OF GROWTH FACTOR POLYPEPTIDES WITH SITES OF ADMINISTRATION OF CELLS THAT SUPPORTS THE §102(E) REJECTION

In the context of the rejection of claims 1-3, 5-8, 33, 63, and 64 as allegedly unpatentable over Weiss under 35 U.S.C.§103(a), the Examiner's Answer states that Weiss fails to "ipsis verbis teach administration of TGF-alpha, "outside the ventricles," via, "intrastriatal administration," and where the site is, "spinal cord tissue and spinal nerve root origins."[37] The Examiner's Answer further stated that Weiss renders obvious administration of the growth factors outside the ventricles "because the reference teaches the relevant sites outside the ventricles that are to be treated by the neural precursor cells and that are stimulated to proliferate, differentiate and migrate via TGF-alpha exposure."

However, as noted above, the Examiner has confused a discussion in Weiss of administering cells to various sites, and a discussion in Weiss of administering growth factor polypeptides **into the ventricles**. Administration of cells to sites of CNS injury does not render obvious claims directed to administration of a TGF-α polypeptide, or a functional fragment thereof, parenterally to a site outside the ventricles, or intrastriatally.

5. THE EXAMINER'S ANSWER ASSERTS THAT WEISS DISCLOSES POSITIVE RESULTS THAT ARE NOT PROVIDED IN THE REFERENCE

The Examiner's Answer stated that "[t]he artisan would expect positive results using the various modifications *given the success of Weiss in providing treatment of Parkinson's disease and spinal cord injury* as exemplified in the '885 patent."[38] (emphasis added)

There is no indication in Weiss that Parkinson's disease was successfully treated. Weiss discusses transplanting neural stem cell progeny or fetal human cells into the striatum of animal models

[37] Examiner's Answer, page 13.

[38] Examiner's Answer, page 19.

of Parkinson's Disease.[39] Weiss states that the neural stem cell progeny were prepared according to the procedures described in Examples 1 and 4. Example 1 of Weiss discusses how the cells were obtained; Example 4 discusses culturing the cells *in vitro* in medium containing EGF or TGF-α, which provided for *in vivo* proliferation of the cells. There is no indication that the cells produced TGF-α in the animal models of Parkinson's disease. Furthermore, the data presented in Weiss merely relate to the location of the transplanted cells in the brains of the animal models. There is no indication that the cells were effective in treating Parkinson's disease.

Weiss provides a prophetic example relating to administration of growth factors into the lateral ventricle in rat model of Parkinson's disease.[40] There are no data presented that would indicate that Parkinson's disease could be treated by administering growth factors into the lateral ventricle.

Similarly, there are no data in Weiss that indicates that spinal cord injury was successfully treated. Weiss provides a prophetic example relating to spinal cord injury.[41] Weiss states that "[n]eural stem cell progeny are prepared and are transplanted into the lumbar lateral funiculus."[42]

6. WEISS' TEACHING AND RESULTS RELATING TO TRANSPLANTATION OF CELLS THAT PRODUCE A GROWTH FACTOR DO NOT RENDER OBVIOUS ADMINISTRATION OF *A GROWTH FACTOR POLYPEPTIDE*

The Examiner's Answer stated that "[a]dministration via transplantation of cells for the production of growth factors such as TGF-alpha is just as effective to administer TGF-alpha as administration of the factor itself and as noted it meets the claim limitations of administration of the polypeptide because both procedures necessarily result in the delivery (administration) of the polypeptide growth factor."[43]

This statement in the Examiner's Answer appears to be based on pure supposition. Cells are not polypeptides. Administering cells is not administering polypeptides. The Examiner has not pointed to any working example in Weiss showing that administration of TGF-α can be accomplished by

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[39] Weiss, Example 45, column 60, lines 36-67.

[40] Weiss, Example 36, column 51, lines 35-50.

[41] Weiss, column 62, lines 4-15.

[42] Weiss, column 62, lines 10-11.

[43] Examiner's Answer, page 22.

administering cells, or even any working example showing administration of TGF-α *per se*. At best, it may "obvious to try" to substitute a TGF-α polypeptide for administration to the sites for cells described by Weiss. However, this is not the standard for obviousness.[44]

In addition, and as discussed above, Weiss emphasized that administration of "growth factors" ***to the lateral ventricle*** provides an ***alternative to prior art methods*** which involve administration ***cells*** in the form of embryonic tissues ***to the striatum***. Even the Weiss reference itself thus acknowledges ***there is a difference in routes of administration for growth factor polypeptides and cells -- and further points to administration of growth factor polypeptides into the ventricles as an alternative to administration of materials outside the ventricles.*** Weiss not only does not disclose the claimed invention, it actually points the skilled artisan in a direction ***away*** *from the claimed invention.*

The Examiner's Answer stated that "[a]lthough the transplantation procedure is achieved via a different process, via administration of cells that make the growth factor, it is well established in patent law that product by process limitations fail to distinguish over product disclosures."[45] Appellants do not understand the relevance of this statement to the claimed invention. The claims are not directed to compositions; they are directed to *methods*. The claims are not directed to a "transplantation procedure"; they are directed to methods of using TGF-α *polypeptides*. The Examiner appears to again attempt to inappropriately equate Weiss' disclosure relating to cells with Weiss' disclosure relating to growth factor polypeptides. As Appellants have set out above, this reasoning is not supported by either the law or the facts.

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[44] See, e.g., MPEP §2145 ("In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted)).

[45] Examiner's Answer, page 22.

II. CONCLUSION

Appellants have presented detailed reasoning and substantial evidence that Weiss neither anticipates nor renders obvious the appealed claims under 35 U.S.C. §102(e) and §103(a), respectively. Additional arguments have been presented during prosecution of the instant claims, in responses to Examiner's Actions and in Appellants' Appeal Brief.

Appellants have also illustrated why the reasoning used by Examiner in support of the rejections of the claims is, at best, not well-founded. The rejections rely on an improper reading of Weiss, an improper use of the disclosure of Weiss which is proscribed by both the law and the disclosure of Weiss itself, and improper interpretation of Appellants specification.

The claimed invention represents a great advance in the field of repair of CNS damage. To the best of Appellants knowledge, there are few or no approved therapies currently available for treatment of persons who are debilitated by injuries or diseases, such as strokes. Weiss, the *only* art upon which the rejections under appeal are based, *fails* to place the claimed invention in the hands of the public.

In view of the remarks set forth above, and those already of record, Appellants respectfully request that all rejections of claims 1-3, 5-8, 33, 63, and 64 be withdrawn, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-263 CIP.

Respectfully submitted,
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